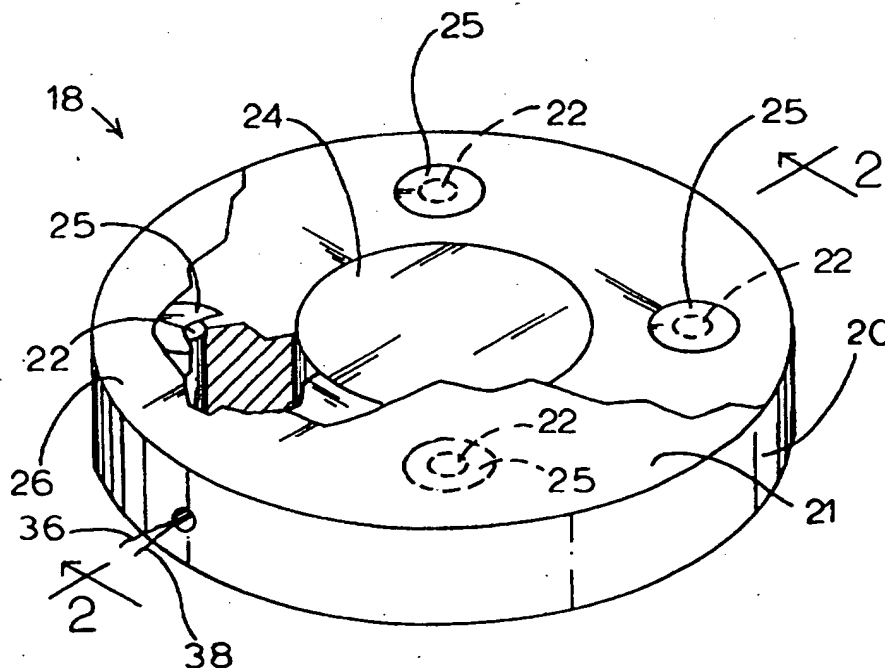




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(54) Title: DEVICE FOR MONITORING CHANGES IN ANALYTE CONCENTRATION



(57) Abstract

The invention provides an electrochemical sensor system for measuring analyte concentrations in a fluid sample. The invention is particularly useful for measuring analytes such as glucose in a patient. An implantable glucose sensor (18) includes a disc shaped body (20) containing multiple anodes (22) on opposing sides of the body (20). Electrodes (22, 24) are connected to a transmitter (130) which transmits radio signals to an external receiver (134) and computer (138) where data is processed to yield glucose concentration figures.

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DEVICE FOR MONITORING CHANGES IN ANALYTE CONCENTRATION

Field of the Invention

5 The invention relates to electrochemical systems for measuring analyte concentration. In particular, the invention involves a sensor including electrodes under a semi-permeable membrane for monitoring analyte concentrations in fluids surrounding the sensor.

Background

10 There are many instances when it is necessary to monitor the concentration of molecules ("analytes") in a fluid. For example, glucose levels must be frequently monitored in persons with diabetes so that appropriate doses of insulin can be administered in a timely manner. Many other analytes are measured commonly in human blood and in other fluids.

15 A variety of methods and devices for measuring analytes in fluids have been devised. One such device, referred to as an electrochemical sensor, typically includes oppositely charged electrodes under a semi-permeable membrane. Depending on what analyte is being monitored, membranes, enzymes and/or other appropriate materials are provided around the electrodes
20 so that analyte reaction and transport from the fluid surrounding the sensor is controlled. Oxidative and reductive reactions take place at or near the electrodes, thus causing electron potentials measured as changes in current which may be correlated to the concentration of analyte in the fluid.

Electrochemical sensors have been used to measure glucose in human blood for a long time. Most of these sensors are designed to measure glucose in a blood sample which has been drawn or extracted from the patient. For patients such as people with diabetes who must test blood glucose levels as often as several times per day, the regular blood drawing process (typically by finger tip puncture) becomes quite cumbersome, messy and even painful. The diabetic must carry special equipment for extracting blood. Some patients fail to test as frequently as they should because of problems associated with the blood extracting process.

Therefore, it has been recognized for a long time that an implanted glucose sensor would offer the important advantage of avoiding the need for repeated blood extraction. However, there are other problems which must be addressed with an implantable sensor. First, there must be a mechanism for accessing raw electrical data generated by the sensor under the patient's skin. Protruding wires are undesirable because they are cumbersome, prone to causing infection and sometimes painful. Accordingly, it is preferable to include a wireless data transmission (telemetry) device coupled to the sensor in a single implantable unit so that no trans-dermal wires are required.

Second, an implanted sensing unit may cause internal trauma, i.e., bruising or bleeding from the patient's routine movement or contact with his or her environment, especially if the sensing unit is large or thick or if it is geometrically shaped with any sharp points or edges.

Another problem associated with implantable sensors is that over time (days and weeks) a cellular coat tends to develop around the sensor which may eventually block the analyte of interest from contacting the electrodes, thus causing the sensor to fail.

5 For these reasons, and perhaps other reasons, researchers in the field have been unsuccessful in their attempts to produce an implantable sensor unit which is capable of functioning satisfactorily for a sufficient period of time to justify the expense and inconvenience of producing and surgically implanting the sensing hardware.

10 A viable implantable glucose sensor should provide reliable performance for at least 1-2 months, preferably three months or more. During its useful life, the device should generate a predictable dose response over a concentration range of approximately 40 to 400 milligrams per deciliter (mg/dl). The device should exhibit a lag time between a concentration change
15 and the resulting signal output of less than 20 minutes, preferably less than 10 minutes. The sensor should be relatively insensitive to potential interfering substances such as ascorbic acid and acetaminophen. The device should be relatively accurate for at least several days after calibration (stability). Glucose measurement with the sensor should be precise to at least within approximately
20 10 mg/dl. The sensor should be incorporated in an implantable unit which is capable of wireless data transmission, and which is dimensioned so as to minimize surgical complication and risk of pain, bruising or other internal trauma.

Summary of the Invention

The objectives stated above are achievable with the device and system of the present invention which includes a device for electrochemically sensing changes in the concentration of an analyte of interest.

5 In one embodiment of the invention, the device includes a sensor body having two opposing sides. Each side of the body includes at least one, preferably several, anode(s) and at least one cathode spaced apart from each other and covered by a membrane which is semi-permeable to the analyte of interest. In a preferred sensor design for measuring glucose, plural anodes are
10 disposed on two opposing sides of a disc-shaped sensor body. The anodes are covered by an enzyme layer including glucose oxidase and an outer semi-porous membrane layer made of a material such as Parylene™ ("PPX") or Chronoflex™ AR ("CAR").

 In another embodiment of the invention, the sensor body contains
15 a plurality of electrode pairs, each pair including an anode and a cathode. The electrode may take the form of points or lines. In one design linear electrodes are arranged in a "spoke-like" configuration. The electrode pairs preferably are disposed on both sides of the body.

 An implantable glucose sensor, according to the present
20 invention, may be electrically coupled to a transmitter which includes a power source, for example a battery. The transmitter is capable of converting data signals from the sensor into corresponding radio signals. A receiver is provided remotely from the sensor for receiving the radio signals. A processor is

connected to the receiver and used to interpret the radio signals, to yield analyte concentration figures.

The present invention also provides a method of making an analyte sensor. A substantially disc-shaped body is provided with two
5 opposing sides. At least one cathode and plural anodes are created on each side of the body. A semi-permeable membrane is deposited on the electrodes. When the method is employed to make a glucose sensor, the enzyme layer including glucose oxidase is created between the anodes and the semi-permeable membrane. An interferent retarding layer may be created between
10 the anodes and the enzyme layer.

Description of the Figures

Figure 1 is a partially cut-away perspective view of an analyte sensor in accordance with a preferred embodiment of the present invention.

Figure 2 is a cross-sectional view of the sensor shown in Figure
15 1.

Figure 3 is a top view of an analyte sensor in accordance with a second embodiment of the present invention.

Figure 4A is a top view of an analyte sensor employing linear electrodes in accordance with a third embodiment of the present invention.

Figure 4B is a partial cross-sectional view of the sensor shown in
20 Figure 4A.

Figure 5 is a top view of another analyte sensor in accordance with a fourth embodiment of the present invention.

Figure 6 is a schematic side view of a glucose sensor including an interferent retarding layer.

Figure 7 is a schematic flow chart of an analyte monitoring system including sensor, electronics, telemetry and computing components.

5 Figure 8 is a flowchart of an analyte monitoring system including multiple sensors linked in parallel to the same data acquisition and processing components.

Figure 9 is a top view of an implantable unit including a glucose sensor and radio telemetry device.

10 Figures 10 and 10A are circuit diagrams illustrating circuitry employed in glucose sensors of the present invention.

Figure 11 is a graph demonstrating the results of an experiment conducted to compare longevity of single and multiple anode sensors.

15 Figure 12 is a graph illustrating the results of an experiment conducted to compare sensor performance pre-implant versus post-explant.

Figure 13 is a graph showing the average glucose dose response and repeatability of eight sensors each of which was coated with PPX.

Figure 14 is a graph showing the average glucose dose response and repeatability (n=3) for a sensor coated with CAR.

20 Figure 15 is a graph presenting the results of an experiment conducted to determine the relative response times (T90s) for eight sensors each of which was coated with PPX.

Figure 16A is a perspective view of a disk-shaped implantable sensor with a circumferential polymer matrix for carrying and slowly releasing a fibrotic capsule interference inhibitor.

Figure 16B is a cross-sectional view of the sensor shown in
5 Figure 16A.

Definitions

An electrode means an electric conductor, which may be an anode or a cathode.

An anode is a positively charged conductor.

10 A cathode is a negatively charged conductor.

A sensor is a device which detects changes in analyte concentration in a fluid surrounding the sensor. A sensor includes an anode and a cathode, chemically modified and physically arranged to produce electric signal changes which can be interpreted by sensing electronics into analyte
15 concentration changes over a specified concentration range.

An analyte is a molecule of interest in a fluid surrounding a sensor.

An electrometer is a device which senses small changes in current and translates amps to volts.

20 A transmitter or radio telemetry device is a device which transmits radio signals.

A receiver is a device capable of receiving radio signals from a transmitter.

A body is a housing for supporting and containing sensor components.

5 A semi-permeable membrane or analyte selective coating is a material which permits controlled transfer of an analyte through the material.

Interfering substances are molecules in the fluid surrounding the sensor, which are potentially detectable by the sensor possibly causing an inaccurate or erroneous analyte concentration determination. An interferent
10 retarding layer is a material employed in a sensor to either physically or chemically neutralize a potential interfering substance, thereby preventing the substance from interfering with the desired analyte concentration determination.

Chronoflex™ AR ("CAR") is a trade name for a carbonate based
15 polyurethane available from Polymedica.

Parylene™ ("PPX") is a trade name for polyparaxylxylene available from Union Carbide.

Description of the Invention

We have invented an analyte sensing system including an
20 implantable sensor which exhibits significantly improved performance characteristics over a longer functional life in comparison to prior sensing systems. Our invention has also resulted in improvements which are useful in non-implantable sensors and other sensing applications. The model for

illustrating important principles of the present invention, as discussed in detail below, relates to implantable glucose sensors.

Prior implantable glucose sensors do not function satisfactorily over a long enough period to justify the cost and complications of implantation.

5 We have observed that increasing the number of anodes, or electrode pairs, or total number of sensors connected in parallel, and by distributing the anodes on different sensing faces of one or more sensors, greatly enhances the functional life span of an implantable glucose sensing system. Our experiments confirm that redundancy enhances sensor unit function. Other problems with prior
10 electrochemical glucose sensors relate to electrical drift and instability. The redundancy of the present invention, i.e., multiple anodes or multiple sensors distributed on multiple faces of one device, appears to significantly reduce such drift. A possible reason for this is that each individual sensing unit may have its own fundamental instability, and that by incorporating multiple sensing units
15 into a single system, an averaging effect tends to cancel out random drift associated with individual sensors.

Figures 1 and 2 illustrate a disc-shaped glucose sensor which has two opposing faces, each of which has an identical electrode configuration. One of the faces can be seen in the partially cut-away perspective view in
20 Figure 1. Sensor 18 includes a disc-shaped body 20. On planar face 21 of sensor 18, four platinum anodes 22 are symmetrically arranged around centrally disposed silver chloride cathode 24. Each anode 22 is covered by an enzyme layer 25 including the active enzyme glucose oxidase and stabilizing

compounds such as glutaraldehyde and bovine serum albumin (BSA). A semipermeable membrane layer 26 covers all of the electrodes and individual enzyme layers. The thickness and porosity of membrane layer 26 is carefully controlled so as to limit diffusion and/or transport of the analyte of interest (glucose) from the surrounding fluid into the anode sensing regions. The mechanism of selective transport of the analyte of interest through the membrane may involve one or more of the following principles: molecular size exclusion, simple mass transfer, surface tension phenomena and/or other chemically mediated processes.

A cross-section of sensor 18 is shown in Figure 2. Sensor 18 has a plane of symmetry SS which is normal to the plane of the figure. Under face 31 of sensor 18 anodes 32 are spaced equidistantly apart from cathode 34. Enzyme layers 35 cover anodes 32. A semipermeable membrane 36, preferably PPX or CAR, covers the enzyme layers and electrodes. Each of anodes 22 and 32 are connected to a common anode wire 36 which leads out of the sensor for electrical connection to an electrometer. Similarly, each of cathodes 24 and 34 are connected to a common cathode lead 38 which leads out of sensor 18 for electrical connection to the electrometer.

Figure 3 shows an alternative embodiment of the invention in which a plurality of electrode pairs are presented on both sides of a disc-shaped sensor. Only one side of the sensor is shown in Figure 3. The enzyme and semipermeable membrane layers are removed to permit viewing of the electrode configuration. Sensor 50 (an "8-in-1 sensor") includes eight electrode

pairs 52, only four of which are shown distributed around surface 53 of sensor 50. Each electrode pair 52 includes an anode 54 spaced apart from a cathode 56. Similar to the first embodiment described, all of anodes 54 are linked to a common anode wire (not shown) which extends outside the body of sensor 50.

5 All of cathodes 56 are connected to a common cathode wire which extends outside sensor 50. The anode and cathode wires leading out of sensor 50 are eventually connected to an electrometer.

Figures 4A, 4B and 5 illustrate a different type of anode and cathode configuration in which each electrode is exposed along a linear path on the sensor surface. In Figure 4A, sensor 60 is formed with troughs 62 and 64 that intersect at right angles in the center of the sensor surface. Within trough 10 62 linear anode 66a runs parallel to linear cathode 68a. Similarly, in trough 64 linear anode 66b runs parallel to linear cathode 68b. The electrodes are insulated from each other in the junction area 69 where the troughs intersect.

15 Figure 4B shows a cross section through trough 62 in the junction area of the sensor. Trough 62 has a corresponding trough 70 on the opposite side of sensor 60. In trough 70, linear anode 72a runs parallel to linear cathode 72b. Anodes 66a and 72a are both connected to common anode wire 74. Linear cathodes 68a and 72b are connected to common cathode wire 76. Anode wire 74 and 20 cathode wire 76 lead out of sensor 60 for connection to an electrometer. The troughs are preferably filled with an electrolyte gel.

As shown in Figure 5, the concept of employing linear electrodes across opposing faces of the sensor can be extended to provide more electrode

sensing area or "spokes". In Figure 5 sensor 80 is essentially the same as sensor 60 (Figures 4A and 4B) except that it has two additional troughs, each containing another pair of parallel linear electrodes. Sensor 80 includes trough 82a, 82b, 82c and 82d, all of which intersect in the center of sensor 80. Each
5 of the troughs 82a-d contains a pair of linear electrodes (anode and cathode) encased in electrolyte gel. All of the linear anodes in sensor 80 are connected to a common anode wire, and all of the linear cathodes are connected to a common cathode wire. Other anode patterns which function effectively include a circle, concentric circles or a spiral.

10 Figure 6 shows schematically a cross section through multiple layers on one side of a sensor. Sensor 100 includes an electrode configuration similar to the embodiment illustrated in Figure 3. Electrode pairs 102a-102d each include a cathode 104a-104d and an anode 106a-106d, respectively.

 An electrolyte gel 107 surrounds the anode-cathode pairs, thus
15 providing a faster and more sensitive response to changes in glucose concentration. The gel may be produced from methacrylate compounds or from collagen. For example, a methacrylate compound may be dissolved in an organic solvent and then deposited around the anode-cathode pairs. The solvent is then evaporated. Phosphate buffered saline with KCl is then added
20 to the gel to swell the methacrylate compound. In the 8-in-1 embodiment (Figure 3), the electrolyte gel is placed over the surface of the electrode pairs and/or the gel is injected into the drilled cylinder in which the electrode pair is

situated. Similarly, in the radial spoke-type embodiments shown in Figures 4 and 5, the troughs may be filled with electrolyte gel.

Layer 110 is deposited immediately on top of the electrodes for the purpose of minimizing or avoiding interference due to the presence of interfering substances which may be present in the sample fluid. Enzyme layer 112 is deposited on top of interferent retarding layer 110. Enzyme layer 112 includes, in the case of a glucose sensor, glucose oxidase, and is applied in a solution of glutaraldehyde and bovine serum albumin (BSA), either by placement of a drop over each electrode pair, or by dip-coating the entire sensing unit, or by spin-coating. Semi-permeable membrane 114 is deposited on top of enzyme layer 112 for the purpose of controlling diffusion of glucose from the sample fluid into the electrode region of the sensor. PPX at a thickness of about 3,000-6,000 angstroms works well for this purpose. The preferred thickness of PPX layer 114 is 4,000-5,000A. Other suitable materials for semi-permeable membrane 114 include CAR and polyurethanes such as Tecoflex™, Techothane™, Carbothane™ and Cook™ composite.

A number of interferents which exist in human plasma, can be oxidized at the anode when connected to sensor electronic circuitry, thus registering a current which interferes with the signal of interest, i.e., signal generated due to the presence of glucose. Potential interferents include, for example, uric acid, ascorbic acid and the common analgesic drug acetaminophen. Interferents tend to pass freely through semi-permeable membrane 114 and enzyme layer 112. The compounds can be blocked from

reaching the electrodes by interfering retarding layer 110 which has a pore size big enough to allow diffusion of hydrogen peroxide (H_2O_2), a product of glucose oxidation in layer 112, yet small enough to exclude compounds such as uric acid, ascorbic acid and acetaminophen from reaching the electrodes.

5 A preferred material for the interferent retarding layer 110 is PPX. PPX is a hydrophobic compound which is applied to the substrate in a vacuum deposition chamber. The deposition process can be carefully regulated to form an interferent retarding layer of precise thickness (5,000-8,000Å) prior to depositing the enzyme layer. CAR also appears to be a suitable material for
10 use as an interferent retarding layer.

 Paired sensors can also be used to provide an alternate method of avoiding interfering currents from oxidizable, non-glucose compounds. For example, a first sensor is a standard sensor with glucose oxidase. The first sensor measures glucose and interfering compounds. A second sensor is the
15 same as the first sensor except it does not have glucose oxidase and thus detects only the interfering compounds. The magnitude of the current from the second sensor is subtracted from the magnitude of the current from the first sensor to yield a signal which represents the glucose concentration independent from interfering substance concentrations.

20 The sensor designs described above can also be modified so that the electrodes detect fluctuations in oxygen concentration which is relatable to glucose concentration. In this approach, the sensor monitors oxygen disappearance instead of hydrogen peroxide appearance. First, the polarity is

changed so that the platinum electrodes (previously referred to as "anodes") become negatively charged with respect to the silver chloride (previously referred to as the "cathode"), i.e., the platinum becomes the cathode and the silver chloride becomes the anode. Second, a membrane is deposited immediately on top of the cathode and anode which is permeable to oxygen but not to larger molecules. The outer membrane and the enzyme layer remain the same. In this configuration, glucose concentration results in a decrease in oxygen concentration at the negatively charged electrode.

Another embodiment of the invention has a modified outer membrane. It is possible that functional longevity of implantable sensors is limited because the outer membrane tends to become "fouled," i.e., plugged or covered by molecules and/or other cellular materials. Accordingly, one adaptation of the invention employs a changing membrane so that the outer membrane can be renewed over time without disrupting operation of the sensor. In the modified sensor, the outer membrane is a solid sheet which can be moved across the face of the sensor where the electrodes are exposed. For example, the membrane can be transferred from one roller to another roller analogous to the way film is transferred inside a camera. A drive mechanism such as a small motor may be included in the implantable unit for driving the rollers.

Figure 7 shows schematically how an implantable glucose sensor is connected in a glucose monitoring system 120. Electrodes in sensor 122 are polarized by polarizing circuit 124. Polarization of the sensor electrodes may

be constant or pulsed. Our experiments have shown improvement in sensor performance stability, i.e., maintaining sensitivity and minimizing drift, when polarization is pulsed. For example, polarization of the sensing electrodes can be pulsed alternately on and off at intervals of 15 milliseconds. It may also be
5 advantageous to alternate polarization, i.e., switch the charge of each electrode at regular intervals.

Sensor 122 is connected to electrometer 126 which senses small changes in current and translates amps to volts. Voltage signals from electrometer 126 are telemetry conditioned and conveyed to transmitter 130 for
10 radio transmission. All of the components within box 132 are implanted as a single unit in the patient.

Externally, radio signals from transmitter 130, indicative of glucose concentrations in the patient's blood, are transmitted to receiver 134. Receiver 134 may be connected to monitor 136 for data monitoring. The same
15 receiver computer or another computer 138 may be used to analyze the raw data and generate glucose concentration information. A printer 140 connected to computer 138 generates hard copies of analyzed data.

The concept of including multiple electrode pairs within a single sensor can be extended to an embodiment where separate sensors are implanted
20 and commonly linked to a single electrometer as shown in Figure 8. For example, eight implantable sensors 150 can be implanted in a patient and linked to a single electrometer 152 and transmitter (not shown). Transmitted signals are received by data acquisition adaptor 154 and acquisition computer 156. By

increasing the number of sensors the overall precision, accuracy and longevity of the system can be greatly enhanced. If one or more anodes (or sensors) fails, the others still provide sufficient data sensing capacity so that the entire unit continues to perform satisfactorily. Various algorithms or averaging protocols can be used to process the multiple data streams.

Figure 9 shows schematically the components of an implantable unit in a glucose sensing system. Implantable unit 160 includes disc-shaped glucose sensor 162 which is connected to electrometer and telemetry conditioning package 164 via anode wire 166a and cathode wire 166b. Radio signals derived from the raw current signals are transmitted from transmitter element 168.

Circuitry

Figure 10 shows custom circuitry structure employed in a glucose sensing system of the present invention. Shown generally at 210 is a glucose servotransmitter suitable for implementation with the present invention. Servotransmitter 210 is configured for transmission of data which is indicative of a sensed enzymatic reaction to a remote receiving source for subsequent processing, the sensing and conveyance of such data being described in detail below.

As shown, servotransmitter 210 includes a sensor 212 (also referred to as a two-electrode sensor) operatively connected between a voltage reference source 214 and an amplifier circuit 216. The output of circuit 216 is buffered at 218 and subsequently provided to a voltage-to-frequency circuit

220, which in the preferred embodiment includes a CMOS 7555 circuit indicated at 220a configured with a resistive and capacitive network which includes two resistors (R9 and R8) and a capacitor (C2). Utilization of CMOS for designing circuit 220 has been found ideal due to its low power consumption aspects which results in longer battery life. The output terminal of circuit 220 is connected via line 222 to an AC-coupled transmitter 224 (also referred to herein as a minimitter) for transmission of data to an external receiving source.

Discussing the above servotransmitter in more detail, circuit 210 is configured for detecting electrons which are generated during an enzymatic reaction, and conveying data which is representative of such detected electrons to an external source for subsequent processing. More specifically, sensor 212 includes two electrodes, a cathode 212a and an anode 212b. Cathode 212a is connected to voltage reference source or circuit 214, and anode 212b is connected to amplifier circuit 216. Voltage reference circuit 214 is made up of three resistors R4, R5, and R6 and a 1.2-volt Zener diode Z1. Resistor R6 is connected at one end to a negative voltage potential, and at the other end to diode Z1 and resistor R4. The other end of resistor R4 is connected to resistor R5, which in turn is connected to diode Z1 as shown. The common node between resistors R4 and R5 is connected to cathode 212a.

Anode 212b is connected via resistors R3, R2, to the inverting terminal of amplifier 216a, and a capacitor C1 is connected between resistors R3, R2 and ground. The non-inverting terminal of amplifier 216a is tied to

ground. A resistor R1 is connected between the output of amplifier 216a and its inverting terminal to provide negative feedback.

The output of amplifier 216a is connected to the non-inverting terminal of amplifier 218a, the output of which is connected to the inverting terminal in a voltage follower configuration for buffering the output of amplifier 216a. A resistor R7 is connected between the output of amplifier 218a and the trigger terminal 2 of the CMOS 7555 circuit.

The CMOS 7555 is configured, with its attendant resistive and capacitive network, as a voltage-to-frequency converter whose output frequency is proportional to its input control voltage. Referring more specifically to the 7555, it may be seen that reset terminal 4 is connected to terminal 8, both of which are connected to a voltage potential which may be referred to as VCC. A resistor R8 is connected between reset terminal 4 and discharge terminal 7. A resistor R9 is connected between discharge terminal 7 and the threshold terminal 6. A capacitor C2 is connected between trigger terminal 2 and ground. Output terminal 3 is connected to the AC-coupled transmitter 224 for transmission of data to a remote location for processing.

Discussing the operation of the above-described glucose servotransmitter, it will be understood that voltage reference circuit 214 develops a potential of -0.6 volts which is used by sensor 212 to cause electrons produced in the vicinity of the sensor to flow, in the form of a generated current, with amplifier circuit 216, which includes operational amplifier 216a configured for feedback as described above. The output of

amplifier 216a is a voltage which is buffered at 218 by operational amplifier 218a, the voltage output of which controls frequency for the trigger terminal of the CMOS 7555 through resistor R7 and frequency selection circuitry C2, R8, and R9. The output terminal 3 of the CMOS 7555 is connected, via line 222, to
5 transmitter 224 for transmission to an external source.

It will be appreciated that the above-described 7555 configuration converts the output of buffer 218 into a frequency which is determined by the voltage at threshold terminal 6. The 7555 serves two functions in the above configuration which are necessary for the transmission of sensed data to a
10 remote location for processing. First, the 7555 provides a 15-msec pulse to key transmitter 224, thereby turning it on and off in accordance with practices which will be understood by those of skill in the art. Second, the 7555 is operable for voltage-to-frequency conversion, which is a measurement of sensor response. This dual function enables the aforementioned data
15 transmission in a manner which will be understood by those of skill in the art.

Preferred component values (resistive and capacitive values) for the above-described servotransmitter 210 are as follows: (1) for voltage reference circuit 214: R4 = 1 meg ohm; R5 = 4.7 meg ohm; and, R6 = 470 kohm; (2) for amplifier circuit 216: R1 = 500 meg ohm; R2 and R3 = 499
20 kohm; and, C1 = 10 pf; (3) for converter circuit 220: R9 = 180 kohm; R8 = 1 meg ohm; and, C2 = 1 microfarad; and, (4) R7 = 4.7 meg ohm.

The above system is referred to as a "two-electrode" system because of the fact that two electrodes are utilized (the anode and the cathode)

in the sensing of electrons produced during a particular enzymatic reaction. Another system which is suitable for sensing produced electrons and conveying data relative to such sensed electrons is a so-called "three-electrode" system which is shown in Figure 10A and described briefly below.

5 In Figure 10A, like or similar elements of the three-electrode glucose servotransmitter 210 are labeled to correspond with the two-electrode elements appearing in Figure 10. The Figure shows a sensor 212, a voltage reference source 214, a voltage-to-frequency converter circuit 220, and a transmitter 224. Voltage reference source 214, voltage-to-frequency converter
10 circuit 220, and transmitter 224 will not be described because the operation of those elements is the same as, or similar to the operation of such elements as they appear in Figure 10.

 Sensor 212 in Figure 10A varies somewhat from its Figure 10 counterpart. Such variations take into account some observations regarding
15 current and voltage control which have been made with respect to the two-electrode system described above, and improve somewhat, the control of such parameters. The three electrode sensor, set forth at 212, includes a counter electrode 212a (which may be formed from silver), a common return electrode 212b (also referred to as a working electrode and which may be formed from
20 platinum), and a voltage probe 212c which may also be termed the reference electrode (and which also may be formed from platinum). Two operational amplifiers 212d, 212e are provided and operatively coupled to the electrodes as shown, in a configuration which provides greater current and voltage control

which, in turn, assists in maintaining the integrity of the electrodes' sensitivity and the ability of the same to detect a produced current which is indicative of an enzymatic reaction. The control is effectuated in a clamped, controlled manner.

5 The three electrode sensor 212 is shown in Figure 10A. Amplifier 212d maintains a voltage which is the same as the reference voltage of -0.6 volts between the reference and working electrodes 212c, 212b respectively. This is accomplished by varying the current at the counter electrode 212a which is in the feedback loop of amplifier 212d. Amplifier 212e
10 maintains the working electrode 212b at virtual ground converting the current to an output voltage, which is buffered at 212f and provided to CMOS 7555 converter circuit 220 for conversion from a voltage to a frequency (in a manner described above), the converter circuit thereafter triggering transmitter 224 in a
15 pre-determinable fashion to transmit sensed data indicative of an enzymatic reaction to a remote location for processing.

Decreasing Fibrotic Capsule Interference

One of the primary reasons why a subcutaneously-implanted sensor eventually loses its ability to measure the concentration of an analyte of interest is that a collagenous capsule forms around the sensor. The capsule
20 eventually loses vascularity and becomes thick and fibrous, thereby substantially blocking the sensor from accessing the analyte present in blood.

There are at least two promising approaches for minimizing fibrotic capsule interference with analyte detection, thereby extending longevity

of an implanted sensor. First, it is possible to prevent or retard capsule formation by slow controlled release of certain collagen deposition inhibitors. Drugs which inhibit collagen formation can be incorporated in a polymer matrix which allows slow release of the drug locally to achieve the desired effect without causing adverse distant systemic effects in the animal or human. For example, collagen inhibitors which can be used for this purpose include corticosteroids such as dexamethasone, relaxin and gamma interferon. A preferred polymer material for carrying and controlling slow release of the drug is polydimethylsiloxane. Corticosteroids can be impregnated in a polydimethylsiloxane matrix so as to provide relatively long-term, slow release of the corticosteroids in the surrounding tissue. It is important, however, that dexamethasone be released in small doses in order to avoid iatrogenic Cushing's syndrome, which is a serious illness caused from systemic excess of corticosteroids. If corticosteroids are released from a sensor for a prolonged period, for example, more than two weeks, we recommend that a patient's serum be tested in order to confirm that adverse systemic effects are avoided.

Another approach for minimizing fibrotic capsule interference with sensor performance, i.e., increasing sensor longevity, is to promote vascularity in the capsule so that the sensor can continue to have access to blood analytes. Accordingly, vascular growth factors can be incorporated in a matrix around the sensor so that the growth factors are slowly released into the surrounding tissue. The released growth factors enhance capillary growth in the collagenous capsule which forms around the implanted sensor. Retention

of capillary perfusion by the capsule enhances sensor function by continuously providing the sensor access to the patient's blood analyte. Examples of capillary growth factors include vascular endothelial growth factor (VEGF) and endothelial cell growth factor (ECGF). Polymer materials which are capable of slowly releasing polypeptide factors such as ECGF and VEGF include poly-l-lactic acid and poly glycolic lactic acid. As with the steroid approach, the growth factor dosage, i.e., quantity and rate of release, must be carefully controlled so that the growth factor's effect is local, not systemic.

A method of employing steroids or growth factors to minimize or avoid fibrotic capsule interference with sensor performance, is to provide for the active agent's slow release from the perimeter of the disk sensor. For example, as shown in Figure 16A, glucose sensor 300 has a carrier layer or matrix 302 such as a tape made of or containing polydimethylsiloxane impregnated with dexamethasone. Tape 302 is attached to outer perimeter edge 304 of disk-shaped housing or body 306 of sensor 300. The width of tape 302 is substantially the same dimension as the width of edge 304, i.e., thickness of housing 306, so that the steroid is released on or near both faces of the sensor.

Time-release steroid compositions have been utilized in the past for other purposes. For example, U.S. Patent No. 5,265, 608 to Lee et al., the entire content of which is hereby incorporated by reference, discloses a steroid eluding electrode in which dexamethasone is incorporated in a polymer matrix which permits slow controlled release of the steroid to control inflammation, irritation and swelling in connection with a device such as a pacemaker.

However, no one has previously employed a time release corticosteroid matrix for inhibiting collagen formation on an implantable analyte sensor.

Sensing Other Analytes

With minor modifications, the sensor designs described above may be used to detect analytes other than glucose. By changing the specific type of enzyme which covers the anode, the sensor can be used to measure many compounds. Several examples appear in Table 1 below.

TABLE 1

ANALYTE	ENZYME
glucose	glucose oxidase
glucose	hexose oxidase
lactate	lactate oxidase
l-methionine	l-amino acid oxidase
l-phenylalanine	l-amino acid oxidase
d-aspartate	d-amino acid oxidase
d-glutamate	d-amino acid oxidase
urate	urate oxidase
ethyl alcohol	alcohol oxidase
methyl alcohol	alcohol oxidase
cholesterol	cholesterol oxidase
ascorbic acid	ascorbate oxidase

In addition to measuring analytes in body fluids, sensors of the present invention can be used to measure the concentration of substrates in other fluids, for example, fruit and vegetable juices, wine, yogurt, etc.

Construction of a Glucose Sensor

A preferred sensor is constructed of epoxy resin in a disc shape, 1.3-centimeters in diameter and 0.2-centimeters in height. Four 36-gauge platinum wires terminate peripherally on one face of the disc (in holes drilled in the resin) and service hydrogen peroxide-sensing anodes. A solid silver cylinder, 0.7-centimeters outside diameter (the cathode), is secured by epoxy resin in the center of the disc. A layer of silver chloride can be deposited onto the surface of the silver by one of several processes. The sensor is preferably double-sided, which may be, for example, two of the four anode sensors configured "back-to-back", making a sensor composed of four anodes and one cathode on each face of the sensor.

Anode and cathode recording wires terminate in an amplifier and polarizing voltage source. An electrometer converts the current signal to a voltage signal and applies a constant polarizing voltage of 0.60 V to the electrodes. Output from the amplifier is routed both to a digital volt meter (Micronta 22-185A, Tandy Corp., Fortworth, TX 76102) and to a strip chart continuous chart recorder (Gould Instruments Model No. 11-2963-300, Valley View, OH 44126). The signal can also be routed directly into a computer by use of a data acquisition board. All of these electrical components can be miniaturized without altering the function.

A working 8-anode sensor (which has been demonstrated to respond to peroxide) then is selected for testing. The sensor is sanded, first with 600 and 1500 grit wet-or-dry, then followed by a polishing with 2000 grit

wet-or-dry. The sensor is rinsed thoroughly in a stream of deionized water (DW) followed by blow drying in a cold nitrogen stream. The sensor is then immersed in an acetone bath and vigorously twirled for 20 seconds to remove any solvents or oils from the surface. The sensor is withdrawn from the acetone bath and is immediately rinsed in a DW stream. The sensor is again blown dry in a cold nitrogen stream, and continues to dry in room air for another 30 minutes.

If it is desired to include an interferent retarding layer, then a layer of PPX (or other suitable membrane material) approximately 5,000-8,000A thick is deposited directly on top of the anodes before depositing any enzyme.

The sanded, cleaned and dried sensor (with or without interferent retarding layer) is enzyme activated with a Glucose Oxidase (GO) ---Bovine Serum Albumin (BSA)--- Glutaraldehyde (GA) matrix prepared from mixing two parts GO+BSA (20mg GO + 5mg BSA with 0.5 gram DW) plus one part GA (2.5% GA diluted with DW). Approximately 2.5 μ l of this solution is applied via pipette directly to each anode. The solution is allowed to dry in room air for one hour. The sensor is then immersed in DW for 15 minutes to remove excess GA, rinsed briefly in a DW stream, and blown dry in a nitrogen stream. The sensor continues to dry in room air for one hour, after which spin-coating with PU (Tecoflex, Tecothane, Cook composite, or CAR) or vapor deposition with PPX (thickness = 3000-5000A) is carried out.

Further miniaturization of the glucose sensor, as described above, will not adversely effect performance of the unit.

Testing, Connecting and Implanting Sensors

Sensors manufactured as described above, are tested the day after they are made by applying a polarizing voltage of 600 mV. The voltage output should stabilize after a one to two hour immersion in a temperature controlled PBS solution (37°C) in the laboratory water bath. The sensor is tested in standard glucose solutions prepared by adding glucose to PBS so that the resulting test solutions (G=glucose), are concentrated in mg/dl as follows:

5 G(0), G(100), G(200), G(300), G(400) and G(500); and in millimolar concentrations as follows: G(0), G(5.6), G(11.1), G(16.7), G(22.2) and G(27.8). The first data point is collected while the sensor is still immersed in PBS and represents the baseline output. After noting the output value, the sensor is moved to G(100) for ten minutes. The process of measuring the speed

10 with which the sensor responds to the increase in glucose allows calculation of T90 (defined T90 below). The sensor is moved to the G(200) standard and the ten minute output value is collected from this standard. All of the following outputs are collected in ascending order in the same manner.

15

An implantable sensor has to satisfy three criteria: (1) it must

20 have a T90 of less than three minutes; (2) it must be dose responsive in the glucose concentration range of 40-400 mg/dl; and (3) it must have adequate sensitivity. The T90 value is measured by using the continuous sensor readout provided by the data acquisition system. The point at which 90% of the

maximum output is reached (after changing from the zero glucose level to the 100 mg/dl level) is recorded as the T90.

A sensor that is acceptable for implant must also be dose responsive, preferably substantially linear over the glucose concentration of 40-
5 400 mg/dl. Minor to moderate non-linearities can be mathematically corrected to allow estimation of glucose level from sensor output data.

If a sensor meets all the previous criteria, it is attached to a transmitter. For example, a suitable transmitter may be obtained from Mini-Mitter which has a custom-built interface circuit between the transmitter and
10 the sensor. The transmitter should have a battery pack which is fully charged.

The sensor can be implanted in the body of animals or humans. The sensor can be implanted subcutaneously, in an artery or vein, intramuscularly, intraperitoneally, in the brain or cerebrospinally. The preferred location is subcutaneous. The sensor can also be used in vitro, for
15 example, in a laboratory to measure glucose concentration or other substrates or analytes in a liquid media.

The transmitter and sensor package are tested in vitro the day of the planned implant procedure. If the results are satisfactory (T90 less than 3 minutes, satisfactorily dose-responsive, adequate sensitivity), then the unit is
20 sterilized, rinsed in sterile saline, and implanted subcutaneously in the recipient (after the appropriate preparation and anesthesia procedures).

Experiments

Experiment 1

We compared the performance of sensors with one anode to the performance of sensors with four anodes. Twelve one-sensor anode sensors were constructed substantially as described above. These sensors were similar to the ones shown in Figure 1 except they only included one anode instead of four, and they only had electrodes on one side of the disc-shaped sensor. All sensors in this experiment were dip-coated with polyurethane (Cook Composites) instead of parylene. Twenty-four-anode sensors were constructed the same as the one-anode sensors except that they included four anodes on one face of the sensor substantially as shown in Figure 1.

The sensors were implanted in rats. Glucose dose response data was collected for each of the sensors at frequent time points after implantation until the given sensor failed to perform satisfactorily. For each sensor, the last check point at which the sensor performed adequately, determined the functional life of that sensor.

Figure 11 shows the results of this experiment. The average longevity for the one-anode sensors was about 4 days. In contrast, the average longevity for the four-anode sensors was about 28 days. This is a highly significant improvement in the functional life of an implanted glucose sensor, which we attribute to the increased number of anodes.

Experiment 2

The purpose of this experiment was to determine in vitro the performance capability in sensors which had failed in vivo. In this experiment, eight of the four anode sensors used in Experiment 1 were tested before
5 implantation (pre-implant), and then tested again after eventually failing to perform and being removed (post-explant) from the rat.

The results of the experiment are shown in Figure 12. In Figure 12 (and Figures 13 and 14), the "Normal Range" includes glucose concentrations which are typically observed in the normal population. The
10 "Dynamic Range" includes the Normal Range plus abnormally high and low glucose concentrations which should be measurable with a glucose sensor. The results show that in vitro the sensors performed as well post-explant as they did pre-implant. This result demonstrates that failure of the sensors in vivo is not due to inactivation or loss of the glucose oxidase enzyme. We noted that over
15 time in vivo a cellular coat tends to envelop the sensor. Before performing the post-explant testing on the sensors, the coats were removed. This suggests that the cellular coat which develops around the sensor may be involved with eventual sensor failure. Since the cellular coat is relatively non-uniform, it is possible to theorize that one of the reasons why longevity is increased with
20 multiple anodes is that the probability of maintaining one or more anodes under a portion of the coat which is minimal enough so that the sensor still performs, is increased by increasing the number or surface area of sensing anodes.

Experiment 3

In Experiments 1 and 2, the sensors were dip-coated in polyurethane (Cook Composites). We subsequently discovered that uniformity and overall performance of the sensors can be improved by using PPX as the
5 outer coat or semipermeable membrane. The purpose of this experiment was to demonstrate glucose dose response and repeatability for eight sensors, each of which was coated with PPX at a thickness of approximately 3800A. As shown in Figure 13, we observed a dose response approaching linearity in the useful measurement range. Test repeatability was also improved with the PPX coated
10 sensors, as shown by the smaller standard deviation margins in comparison to those shown in Figure 12.

Experiment 4

This experiment was similar to Experiment 3 except instead of using PPX as the semipermeable outer membrane, CAR was used. Eight-
15 percent CAR was spin-coated over the surface of the sensor for 2.5 minutes at 4,000 RPM. The sensor was tested in vitro at various glucose concentrations in 3 successive runs. The data is shown in Figure 14. The dose response over the useful measurement range approached linearity with a higher slope in comparison to slopes obtained with PPX and dip-coated sensors. We also
20 noted a relatively small standard deviation on repeat tests with the CAR coated sensors.

Experiment 5

This experiment was performed in vitro with PPX coated eight anode (four on each side) sensors to determine how rapidly the sensors respond to changes in glucose concentration (T90). Six sensors were constructed with
5 PPX outer coats of 3000-5000A. Results of this experiment are shown in Figure 15. Each of the sensors responded with a T90, i.e., time to reach 90-percent of ultimate current output for a given change in glucose concentration, in less than one minute. This is a faster response time than we had observed previously with polyurethane dip-coated sensors.

WE CLAIM:

1. A device for electrochemically sensing changes in the concentration of an analyte of interest comprising
a body having a pair of spaced facial expanses, each expanse of the body including at least one anode and at least one cathode spaced apart from each other and covered by a membrane which is semi-permeable to the analyte of interest.
2. The device of claim 1 wherein the analyte of interest is glucose.
3. The device of claim 2 wherein each expanse is at least partially covered by an enzyme layer including glucose oxidase between the anode and the membrane.
4. The device of claim 1 wherein the membrane comprises polyparaxylylene.
5. The device of claim 1 wherein each expanse of the body includes a plurality of anodes.

6. The device of claim 5 wherein each expanse of the body has a plurality electrode pairs, each electrode pair including one anode and one cathode.

7. The device of claim 6 wherein each expanse of the body has four electrode pairs.

8. The device of claim 7 wherein the body is disk-shaped.

9. The device of claim 3 wherein each expanse of the body has an interferent retarding layer between the anode and the enzyme layer.

10. A device for electrochemically sensing changes in the concentration of an analyte of interest comprising

a body including at least one anode and at least one cathode, and
a membrane comprising polyparaxylxylene or a carbonate-based polyurethane covering the anode.

11. The device of claim 10 further comprising a layer including glucose oxidase disposed between the anode and the membrane, the device being capable of sensing changes in glucose concentration of a fluid surrounding the device.

12. The device of claim 10 wherein the body has two opposing sides, each side of the body having at least one anode and at least one cathode.

13. The device of claim 12 wherein each side of the body has a plurality of anodes.

14. The device of claim 13 wherein each side of the body has a plurality of cathodes, each cathode being paired with one of the anodes.

15. A device for electrochemically sensing the concentration of an analyte of interest comprising

a body having a plurality of electrode pairs, each pair including an anode and a cathode.

16. The device of claim 15 wherein the body has two opposing sides, the electrode pairs being distributed on both sides of the body.

17. The device of claim 16 wherein the body is disk-shaped.

18. The device of claim 16 wherein each side of the body has at least four electrode pairs.

19. The device of claim 15 wherein the anodes lead to a common anode conductor and the cathodes lead to a common cathode conductor.

20. The device of claim 15 wherein the analyte of interest is glucose and each anode is covered with an enzyme layer comprising glucose oxidase.

21. An implantable device for electrochemically sensing changes in the concentration of an analyte of interest, and transmitting signals indicative of the concentration changes, comprising

a transmitter including a power source,

a sensor electrically coupled to the transmitter, the sensor including a disk-shaped body having two opposing sides, each side of the body having a cathode and a plurality of anodes, whereby the combined transmitter and sensor can be implanted in a mammal for wireless transmission of data indicative of analyte concentration to an external receiver.

22. The device of claim 21 wherein the analyte of interest is glucose.

23. The device of claim 22 further comprising
an enzyme layer comprising glucose oxidase covering the anodes,
and
a membrane semi-permeable to glucose covering the enzyme
layer.

24. The device of claim 21 further comprising an amplifier
and an electrometer, the cathodes and anodes from the sensor being connected
to the amplifier and the electrometer converting current signals into voltage
signals before transmitting corresponding data signals to an external processing
device.

25. The device of claim 21 further comprising an analog-to-
digital converter connected to the sensor for converting analog signals
indicative of current changes into digital signals prior to transmitting
corresponding data to an external receiver.

26. An analyte concentration monitoring system comprising
a sensor including a body having two opposing sides, each side of
the body having at least one cathode, plural anodes and a semi-permeable
membrane covering the anodes, the sensor being capable of generating analog
data signals indicative of analyte concentration in a fluid surrounding the
sensor,

a transmitter including a power source, the transmitter being
electrically coupled to the sensor and capable of converting the data signals into
corresponding radio transmission signals

a receiver for receiving the radio transmission signals at a remote
location.

27. The system of claim 26 further comprising a processor
connected to the receiver for interpreting and converting the radio transmission
signals into analyte concentration information.

28. A method of making an implantable analyte sensor
comprising

providing a body having two opposing sides,

creating at least one cathode and plural anodes on both sides of
the body, and

depositing a semi-permeable membrane on the cathodes and
anodes.

29. The method of claim 28 wherein the analyte is glucose, further comprising depositing an enzyme layer including glucose oxidase on the anodes before the step of depositing the semi-permeable membrane.

30. The method of claim 28 comprising depositing a layer of polyparaxylxylene or Chronoflex[®] AR on the enzyme layer.

31. The method of claim 28 comprising forming the body in the shape of a disk.

32. The method of claim 29 further comprising electrically coupling the sensor to a radio transmitter.

33. The method of claim 32 further comprising
implanting the sensor and transmitter into a mammal,
sensing glucose concentration changes,
transmitting corresponding radio signals to a remote receiver, and
processing and interpreting the radio signals into glucose
concentration data.

34. A system for monitoring analyte concentrations in the blood of a mammal comprising

an organization of implantable sensors, each sensor including an anode and a cathode covered by a membrane which is semi-permeable to the analyte.

35. The system of claim 34 wherein the analyte is glucose, further comprising an enzyme layer between the anodes and the membrane.

36. The system of claim 34 further comprising a body substantially containing all of the sensors.

37. The system of claim 36 wherein the body is substantially disk shaped and has two opposing sides, the sensors being disposed on both sides of the body.

38. The system of claim 37 wherein each side of the body has four sensors.

39. The system of claim 34 further comprising a plurality of bodies, each sensor being provided in a separate body.

40. The system of claim 34 wherein all anodes lead to a common anode conductor and all cathodes lead to a common cathode conductor.

41. A device for sensing changes in the concentration of an analyte of interest comprising
a body,
an analyte detection mechanism contained within the body, and
a fibrotic coat interference inhibitor in close proximity to the body for decreasing interference with analyte detection due to formation of a fibrotic coat around the body.

42. The device of claim 41 wherein the analyte is glucose.

43. The device of claim 41 wherein the inhibitor has the property of decreasing the rate of collagen deposition on the body.

44. The device of claim 41 wherein the inhibitor has the property of increasing vascularity in a fibrotic coat.

45. The device of claim 41 wherein the inhibitor is a steroid.

46. The device of claim 41 wherein the inhibitor is a vascular growth factor.

47. The device of claim 45 wherein the inhibitor is selected from the group consisting of dexamethasone, relaxin and gamma interferon, or mixtures thereof.

48. The device of claim 46 wherein the inhibitor is selected from the group consisting of vascular endothelial growth factor, endothelial cell growth factor, and mixtures thereof.

49. The device of claim 41 wherein the inhibitor is incorporated in a polymer matrix which provides controlled relatively constant release of the inhibitor over time into tissue surrounding the body.

50. The device of claim 49 wherein the polymer matrix includes a material selected from the group consisting of polydimethylsiloxane, poly-L-lactic acid, polyglycolic lactic acid and mixtures thereof.

51. The device of claim 50 wherein the polymer matrix is in the form of a tape impregnated with the inhibitor.

52. The device of claim 41 wherein the body is substantially disk shaped.

53. The device of claim 52 wherein the body has a peripheral edge, the inhibitor being impregnated in a time-release polymer matrix associated with the peripheral edge of the body.

54. The device of claim 41 wherein the inhibitor is dexamethasone.

55. The device of claim 49 wherein the inhibitor comprises dexamethasone and the polymer matrix comprises polydimethylsiloxane.

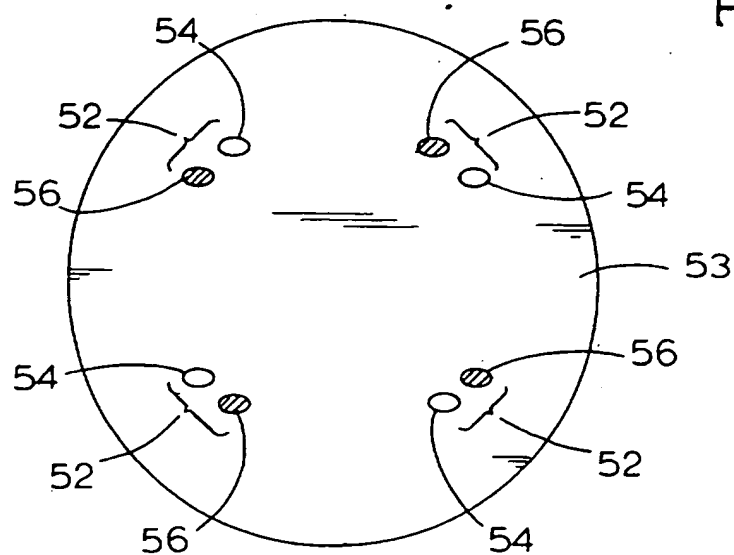
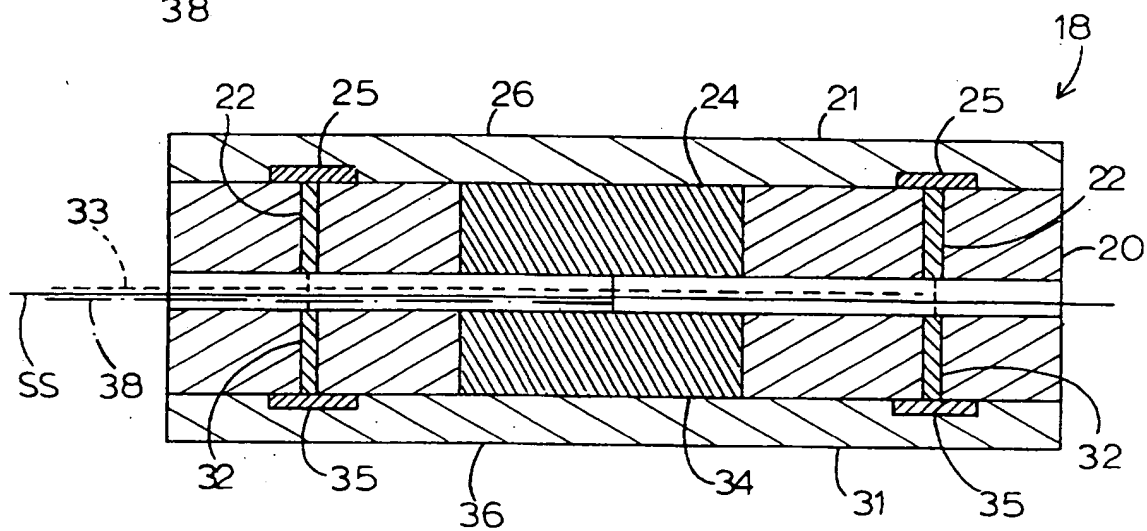
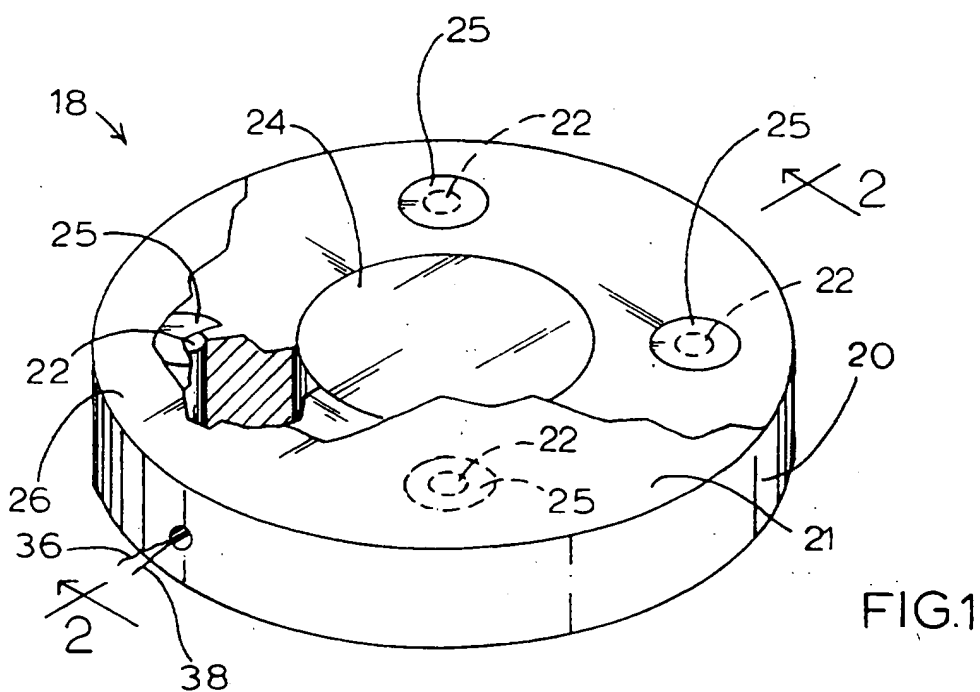
56. The device of claim 41 wherein the body has a pair of spaced facial expanses, each expanse of the body including at least one anode and at least one cathode spaced apart from each other and covered by a membrane which is semi-permeable to the analyte of interest.

57. The device of claim 56 wherein the analyte of interest is glucose.

58. The device of claims 1,2,3,4,5,6,7,8 or 9 further comprising a fibrotic coat interference inhibitor in close proximity to the body for decreasing interference with analyte detection due to formation of a fibrotic coat around the body.

59. The device of claim 58 wherein the inhibitor is a corticosteroid or a growth factor.

60. The device of claim 41 wherein the effective dose of inhibitor is large enough to significantly decrease interference with analyte detection caused by fibrotic capsule formation, but small enough to avoid adverse systemic effects.



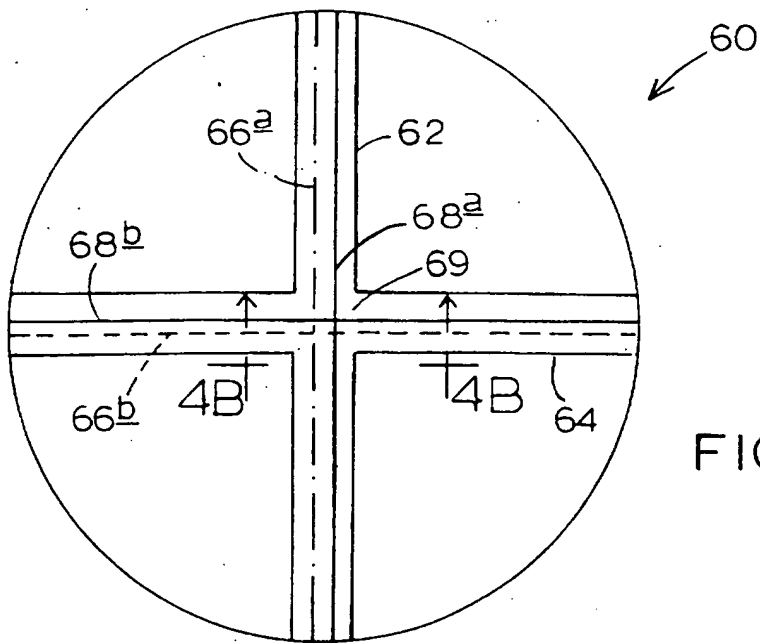


FIG. 4A

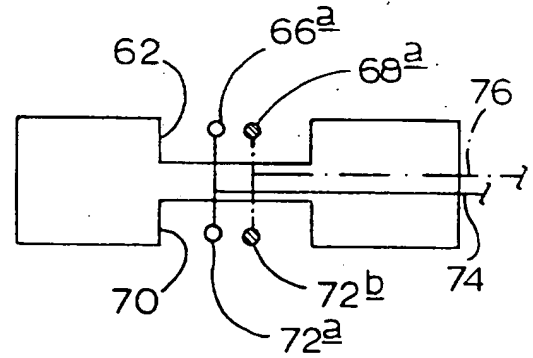


FIG. 4B

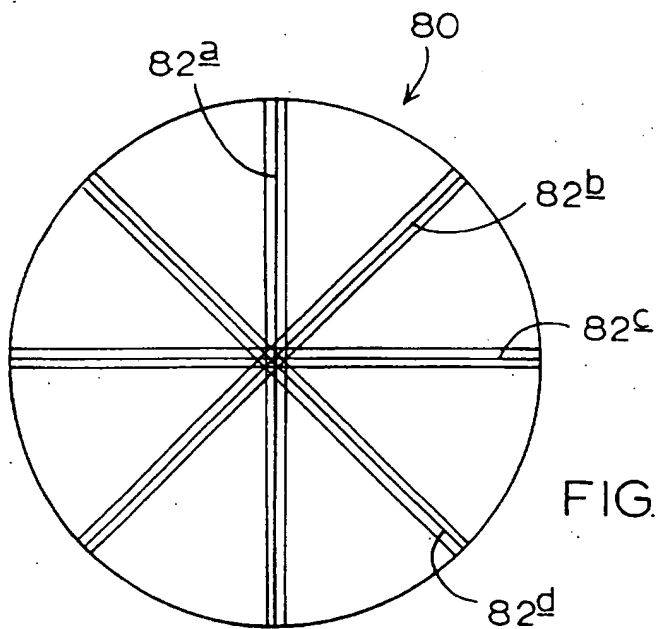


FIG. 5

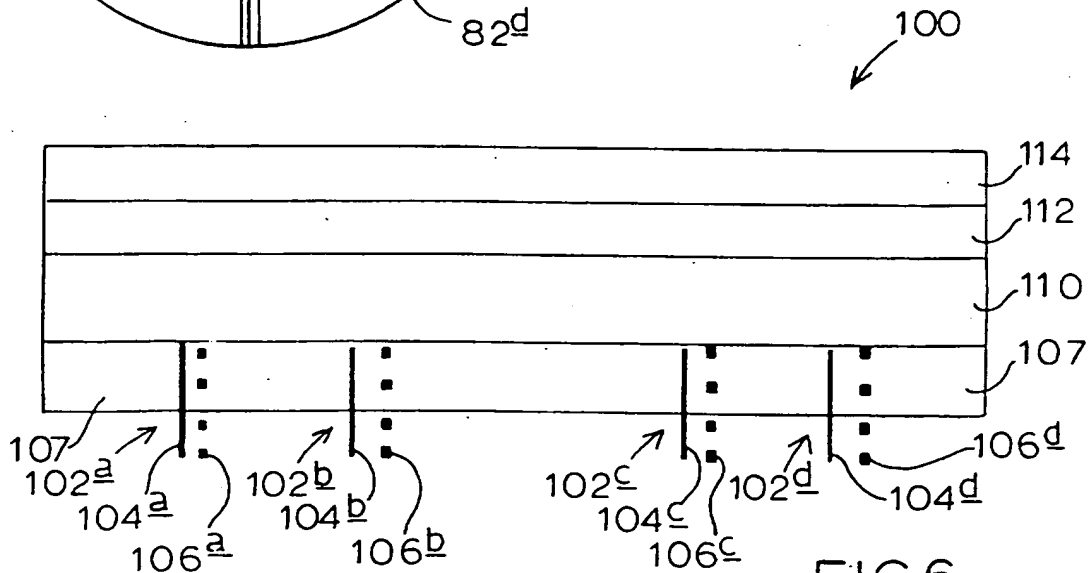
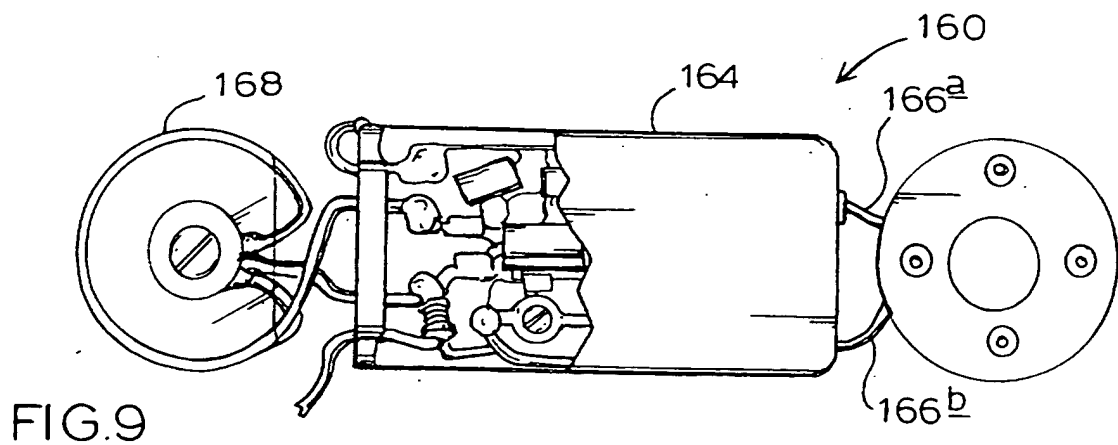
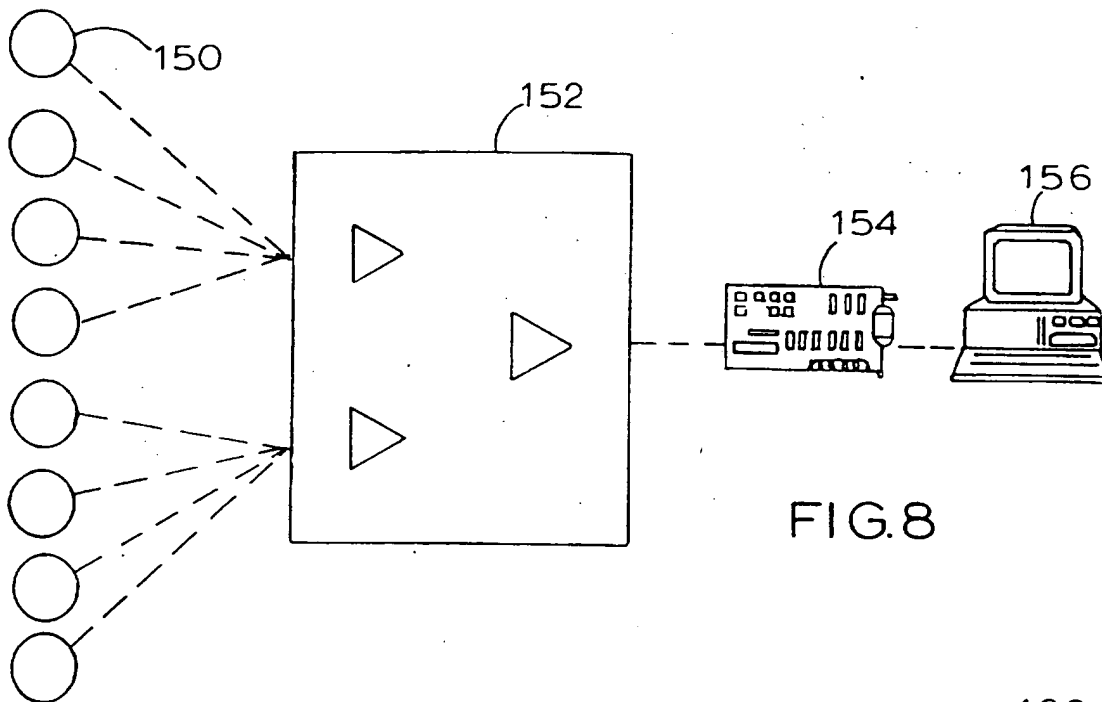
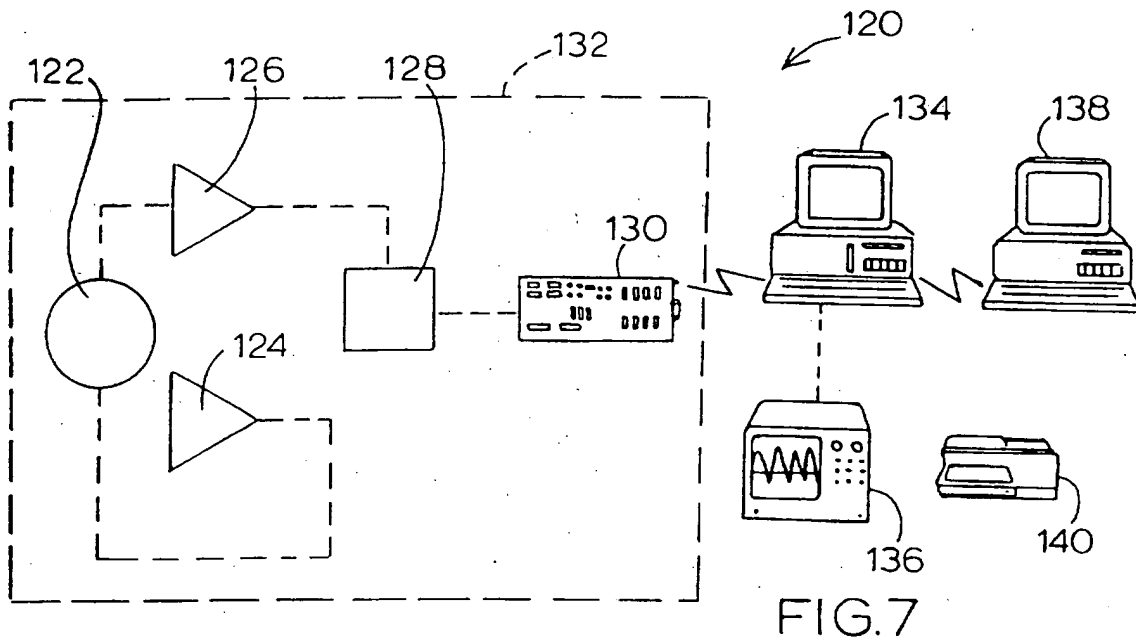


FIG. 6



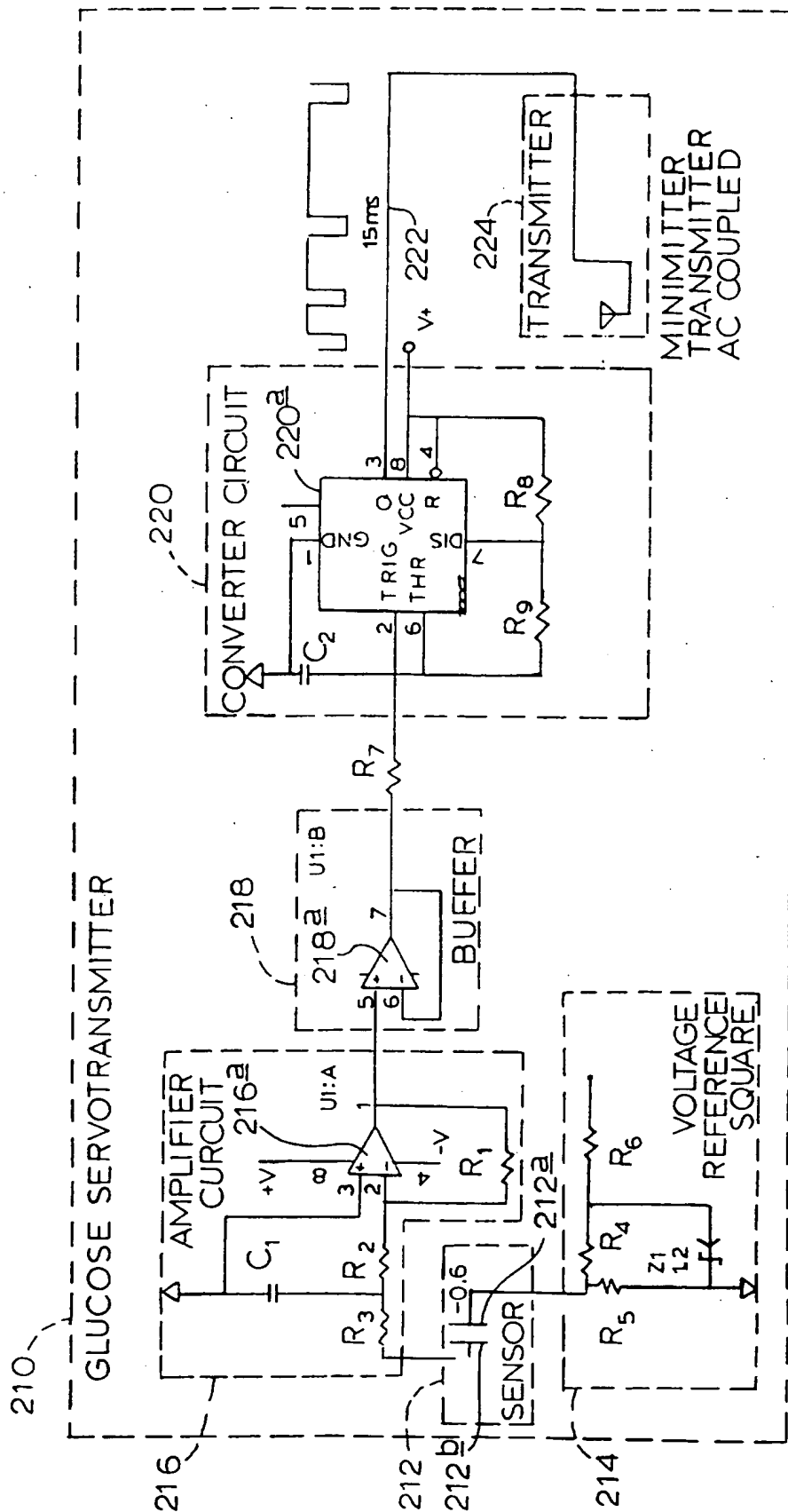


FIG.10

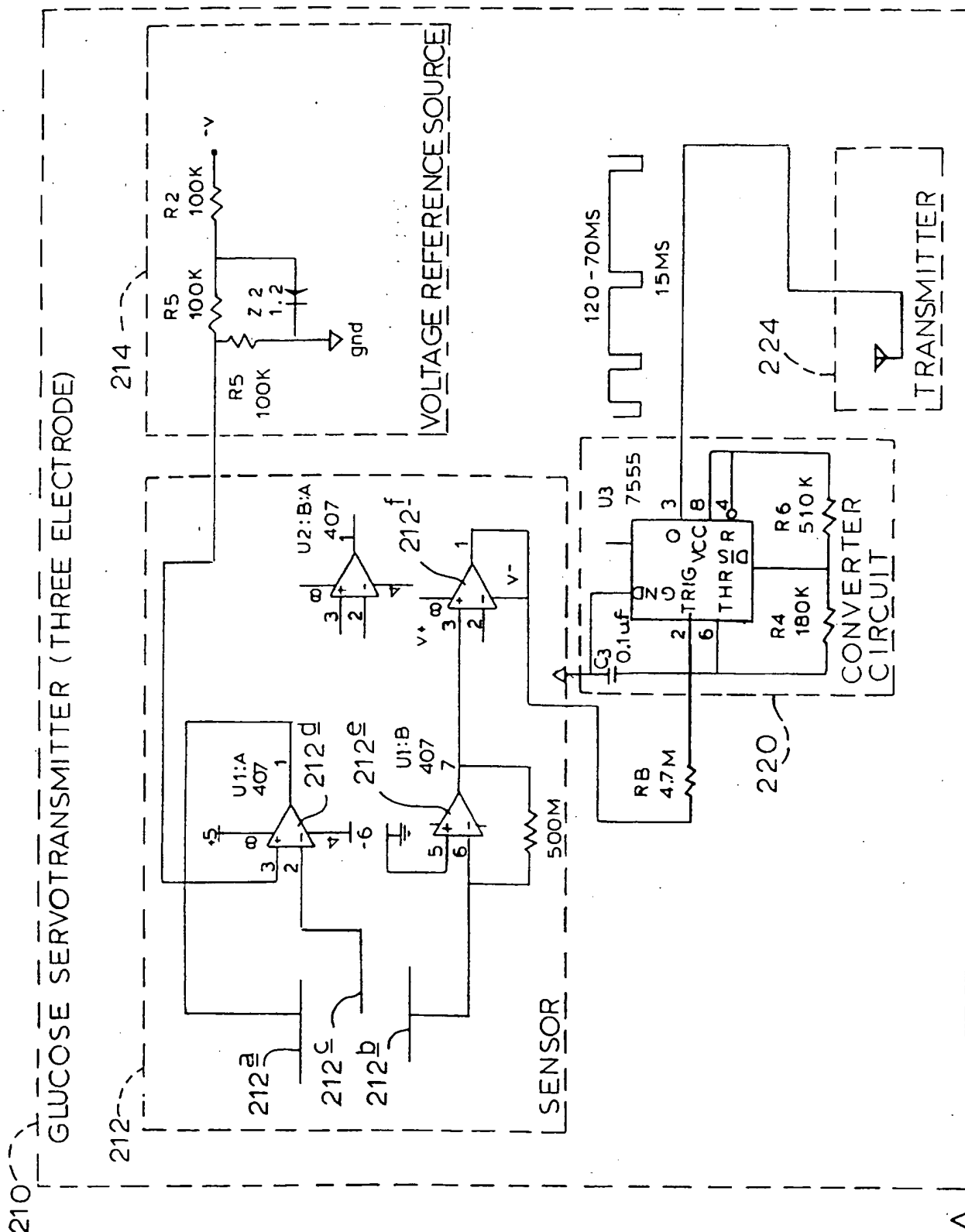


FIG.10A

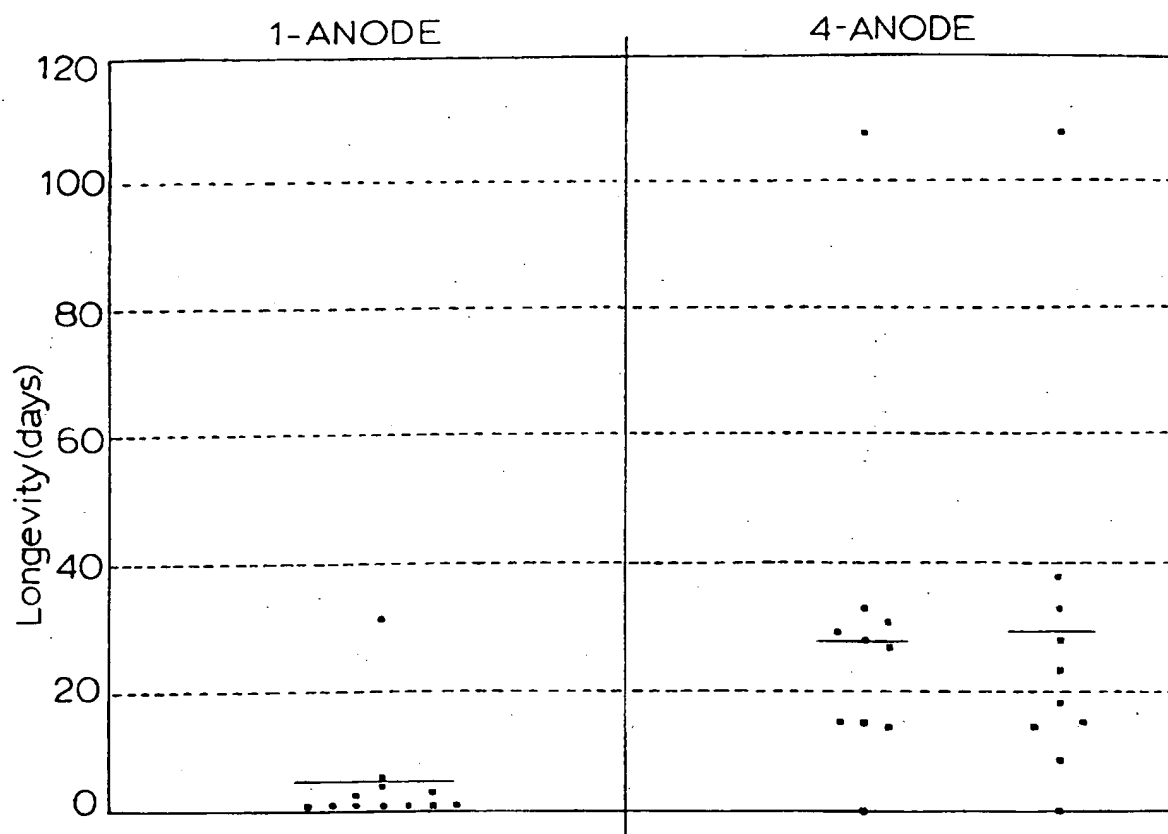


FIG.11

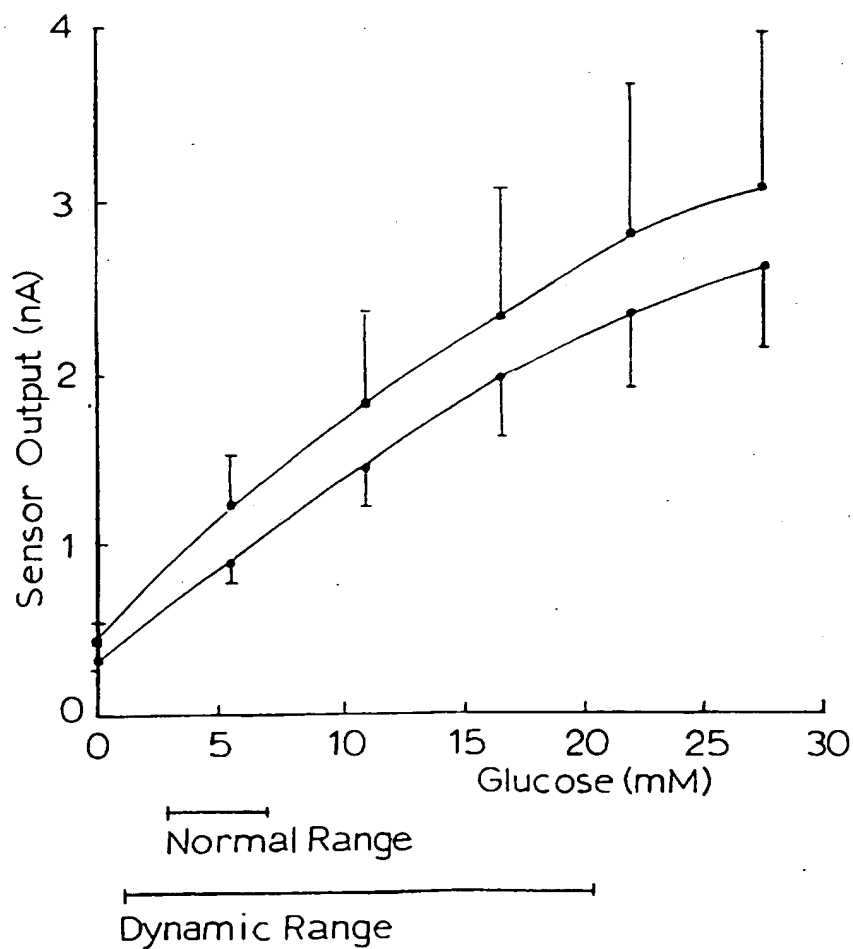
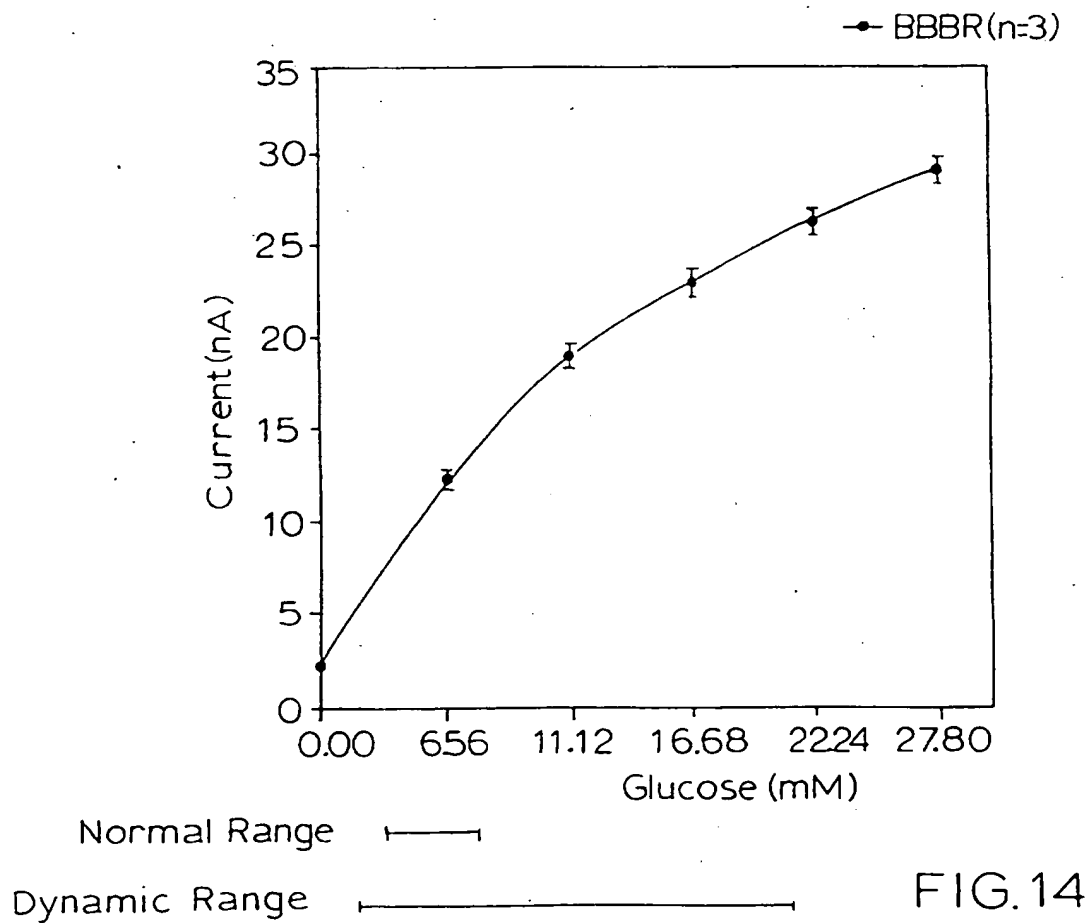
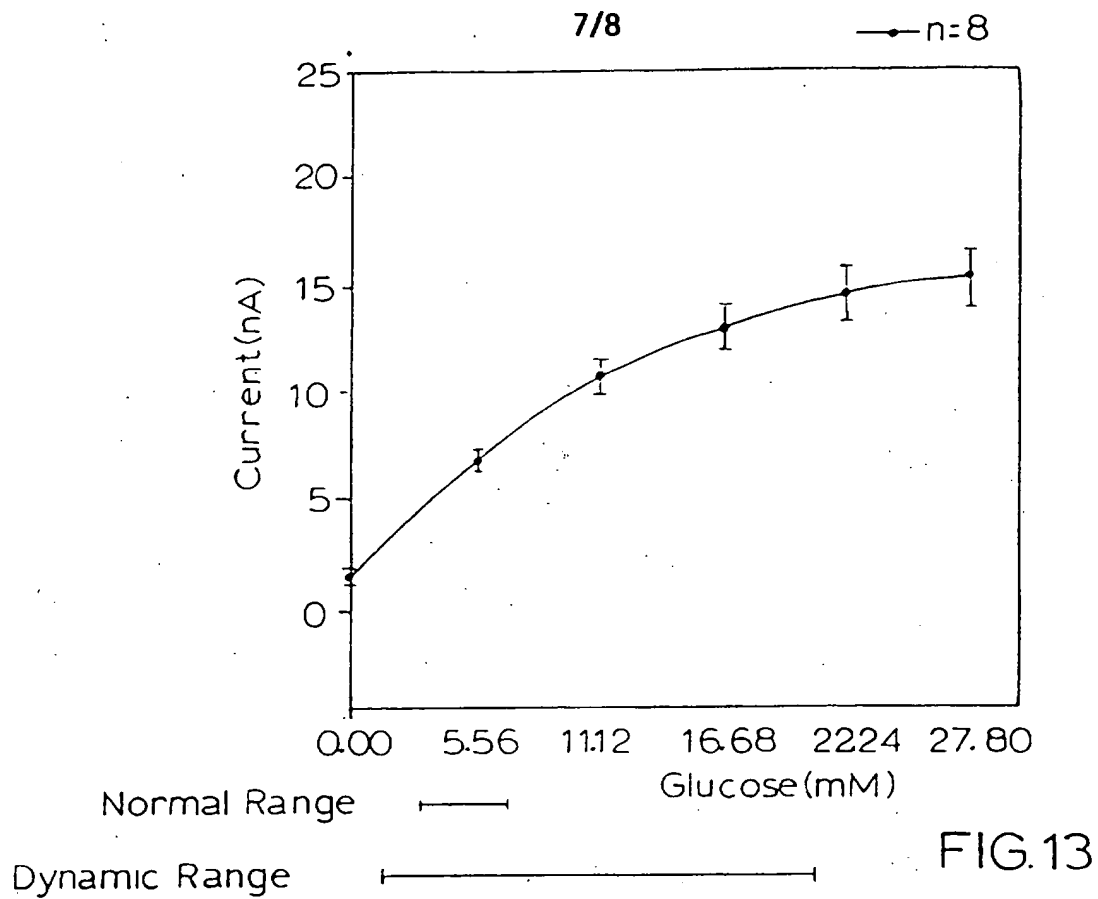


FIG.12



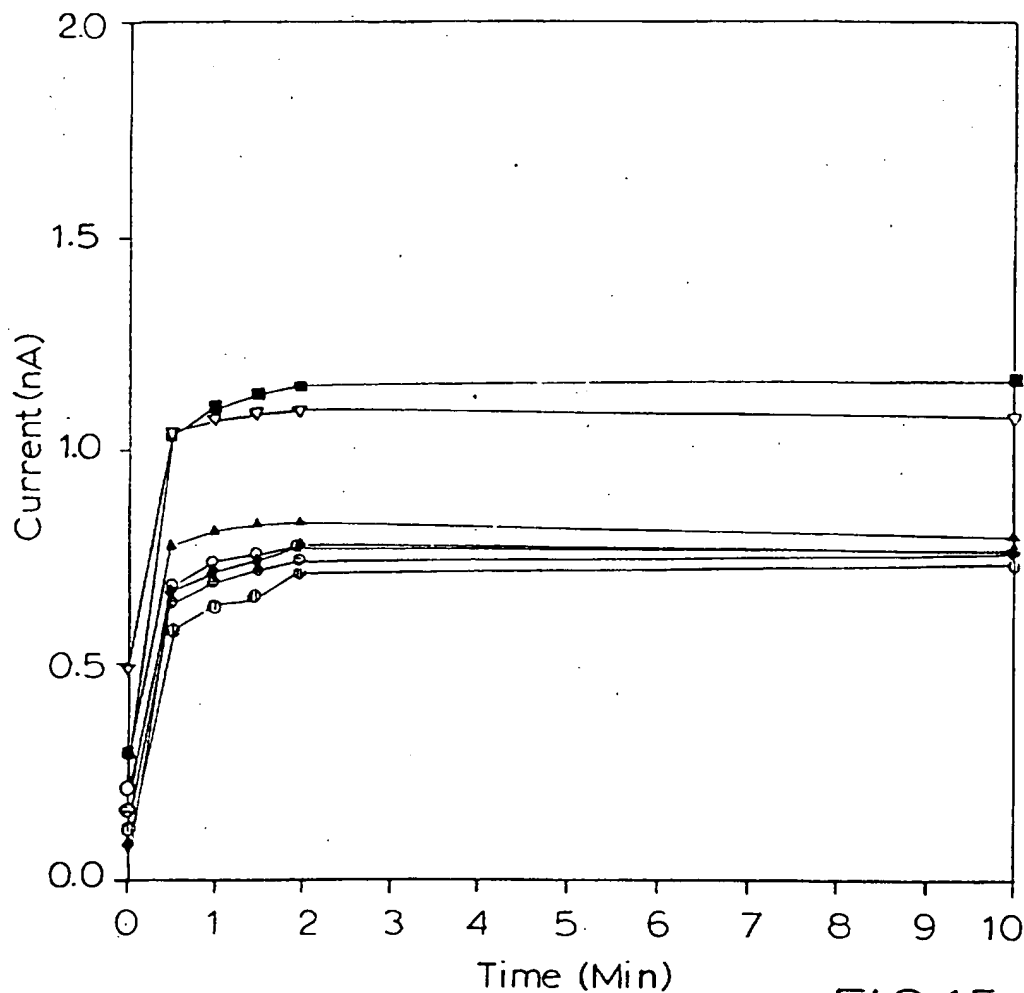


FIG 15

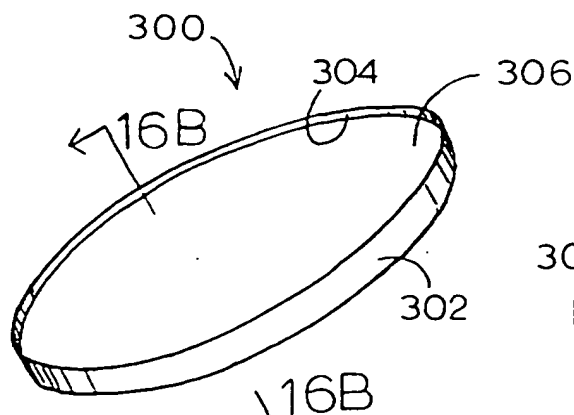


FIG.16A

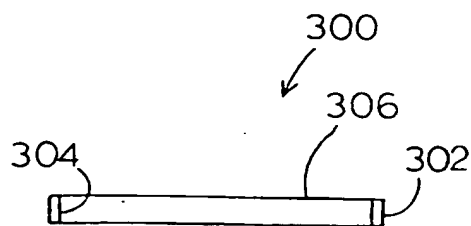


FIG.16 B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/18724

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 204/403, 412, 415; 128/632, 635, 637, 899, Dig. 8; 435/4, 14, 69.2, 183, 288, 291, 800, 811, 817; 604/11, 19, 890.1, 891.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,262,305 A (HELLER ET AL) 16 NOVEMBER 1993, see col. 1, lines 46-66; col. 2, lines 57-68.	1-20
Y	US 5,264,103 A (YOSHIOKA ET AL) 23 NOVEMBER 1993, see Figures 9, 11, and 12; col. 13, lines 10-68.	1-20
Y	US 5,322,063 A (ALLEN ET AL) 21 JUNE 1994, see col. 4, lines 39-46.	1-20
Y	US 4,909,908 (ROSS ET AL) 20 MARCH 1990, see col. 5, lines 40-54 and col. 8, lines 34-50.	1-20
Y	US 4,935,345 (GUILBEAU ET AL) 19 JUNE 1990, see col. 8, lines 24-44 and col. 12, lines 60-68.	1-20

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

26 JANUARY 1997

Date of mailing of the international search report

1 8 MAR 1997

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
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Authorized officer


 BRUCE BELL

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/18724

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,324,518 A (ORTH ET AL) 28 JUNE 1994, see abstract; col. 4, line 60 - col. 5, line 2.	41-60
Y	US 5,391,164 A (GIAMPAPA) 21 FEBRUARY 1995, see abstract; col. 2, lines 23-56; col. 4, lines 38-63; col. 8, lines 41-59; and col. 9, lines 5-31.	41-60
Y	US 5,399,361 A (SONG ET AL) 21 MARCH 1995, see abstract; col. 4, lines 17-24, 42-55; col. 5, lines 3-5.	41-60
Y	US 4,979,959 A (GUIRE) 25 DECEMBER 1990, see abstract; col. 2, line 57 - col. 3, line 2; col. 4, lines 28-46 and Table 1.	41-60

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/18724

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-20 and 41-60

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/18724

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

G01N 27/26; A61B 5/00, 5/05, 19/00; C12Q 1/00, 1/54, 21/06; C12N 9/00, 1/00, 1/20; C12M 1/40, 1/34; A61F 13/20; A61N 1/30; A61K 9/22

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

204/403, 412, 415; 128/632, 635, 637, 899, Dig. 8; 435/4, 14, 69.2, 183, 288, 291, 800, 811, 817; 604/11, 19, 890.1, 891.1

BOX II: OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I (Claims 1-20 and 41-60) relates to a device for electrochemically sensing changes in the concentration of an analyte of interest.

Group II (Claims 21-25) relates to an implantable device for electrochemically sensing changes in the concentration of an analyte of interest.

Group III (Claims 28-33) relates to a method of making an implantable analyte sensor.

Group IV (Claims 34-40) relates to a system for monitoring analyte concentrations in the blood of a mammal.

The inventions listed as Groups II-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The Groups II - IV relate to the invention having to be implantable or having transmitter and receiver capabilities to receive signals from the sensor from a remote location. This places the search for the device and method of making in different locations from that of the device as claimed in the Group I invention.